The role of m6A methylation in abdominal aortic aneurysms: Mechanisms, progress and future perspectives (Review)

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Abstract. Abdominal aortic aneurysm (AAA) is a type of cardiovascular disease. Sudden aortic rupture and subsequent bleeding are the main causes of mortality due to AAA. N6-methyladenosine (m6A) methylation, the most common epitranscriptomic modification in eukaryotic mRNAs, has a key role in the regulation of gene expression. m6A methylation markedly influences the development and progression of AAA. The present review highlights the mechanism of m6A methylation in AAA, including current research progress and future prospects. From a mechanistic perspective, m6A methylation exerts its influence on AAA-related genes by modulating the post-transcriptional levels of RNA, thereby impacting the pathological process of AAA. In terms of clinical applications, the mechanisms by which m6A methylation regulators influence their development and progression in AAA involve multiple target genes and signaling pathways. These regulatory factors affect inflammatory immunomodulation, cell proliferation, apoptosis and endogenous processes by modulating the m6A modification status of target genes and the activity of immune-related signaling pathways. Therefore, for the prevention and treatment of AAA, current therapeutic strategies should comprehensively consider the interactions and synergistic regulation among m6A methylation regulators to reveal the integrated effects of the entire regulatory network in AAA development. Consequently, a more comprehensive understanding of the precise mechanisms of m6A methylation in AAA should be attained, which will support the development of innovative therapeutic strategies aimed at m6A methylation and establish a basis for the early diagnosis and treatment of AAA.

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Abbreviations: AAA, abdominal aortic aneurysm; ALKBH5, alkylated DNA repair protein alkB homologue 5; CCD2, cell division cycle 2; CCL2, C-C motif chemokine ligand 2; circRNA, circular RNA; CRP, C-reactive protein; CT, computed tomography; ECM, extracellular matrix; FTO, fat mass and obesity-associated protein; GEO, gene expression omnibus; HASMC, human aortic smooth muscle cell; IL, interleukin; ILT, intraluminal thrombus; lncRNA, long non-coding RNA; METTL3, methyltransferase 3; m6A, N6-methyladenosine; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; Th, T helper; UTR, untranslated region; VSMC, vascular smooth muscle cell; VIRMA, Vir-like m6A methyltransferase-related protein; WTAP, Wilms tumor 1-associating protein; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; TRMT112, tRNA methyltransferase subunit 11-2; YTH, YTH domain family; YTHDF, YTH N6-methyladenosine RNA binding protein F; YY1, YinYang-1; miR, microRNA; SIRT1, sirtuin 1; RIP3, receptor-interacting serine/threonine-protein kinase 3; NK, natural killer; MMP, matrix metalloproteinase; NAP1L, nucleosome assembly protein 1-like; pri-mRNA, primary miRNA; pre-miRNA, precursor hairpin; DGCR8, Drosha-DiGeorge critical region-8

Key words: abdominal aortic aneurysm, m6A methylation, inflammation, immune response, cell proliferation and apoptosis, microRNA, circRNA

Contents

1. Introduction

An aneurysm is defined as a permanent, irreversible, localized dilatation of a blood vessel (1). The term abdominal aortic aneurysm (AAA) is defined as an anomalous dilation of the infrarenal abdominal aorta measuring ≥3.0 cm. A reduction in the thickness of the abdominal aorta wall can cause it to bulge, resulting in a permanent and progressively expanding focal dilation (2,3). The prevalence of AAA in developed countries is estimated to be between 2 and 8%. If left untreated, it can progress to rupture and become life-threatening, with a mortality rate of ≤80% (4). Treatment of AAA is dependent on a number of factors, including the size, location and rate of expansion of

the aneurysm. In cases of small AAAs, the recommendation is to conduct long-term imaging surveillance, such as ultrasound or computed tomography (CT) scans, to confirm that the aneurysm does not enlarge. An AAA with a diameter >5.5 cm in men and 5.0 cm in women, or one that expands swiftly (0.5 cm in 6 months or >1.0 cm in 1 year), should be monitored, as it is at an increased risk of rupture. Repair is usually recommended in such cases. Treatment options include open surgical repair or endovascular aortic aneurysm repair (5). Randomized trials have demonstrated that for AAA ≤5.5 cm, surgical treatment has no advantage when compared with close monitoring in terms of survival (6). Surveillance programs have been shown to be efficacious, but the associated costs can place a marked financial burden on healthcare systems (7), making it particularly important to investigate alternatives. The identification of biomarkers associated with aortic diameter and AAA growth may prove beneficial in identifying patients who require additional monitoring. Furthermore, biomarkers associated with AAA may represent potential targets for future therapeutic interventions (7). Nevertheless, there are insufficient efficacious medical therapies to either prevent the formation of AAA or to constrain aneurysm growth subsequent to diagnosis. This is due to the incomplete understanding of the mechanisms underlying the formation of AAA. To the best of our knowledge, the majority of previous studies have identified advanced age, male sex, tobacco smoking, hypertension and family history of AAA as the most notable risk factors for AAA (8,9). However, as the smooth muscle cells of the abdominal aorta originate from the splenic mesoderm, the pathogenesis of AAA is distinct from other forms of aortic aneurysms (10). Genetic regulation of gene expression has been well described in various types of human tissue, and several studies have emphasized the important role of genetic factors in the development and progression of AAA (9,11). Genome-wide association studies (GWAS) have pinpointed numerous single nucleotide polymorphisms (SNPs) linked to AAA in both coding and non-coding regions of the genome. These SNPs specific to AAA and their associated genes have been associated with pathological factors, such as extracellular matrix (ECM) organization, inflammation, lipid metabolism, oxidative stress and smooth muscle cell function during AAA development, suggesting that some of the pathological features of AAA may originate from genetic abnormalities (11,12). DNA methylation is an inheritable epigenetic change that takes place at the CpG islands of gene promoters, leading to transcriptional silencing and the modification of cytosine by DNA methyltransferase. The most notable effect of DNA methylation on AAA risk is the disruption of gene transcription related to aneurysms, and it may be a sensitive epigenetic modification (13). Furthermore, epigenetic mechanisms, including DNA methylation, post-translational histone modifications and non-coding RNAs, result in dysregulated aneurysm gene expression levels. Nonetheless, these mechanisms do not lead to substantial sequence variation, unlike genetic causes. Research involving human tissue samples and animal models has revealed that mRNA transcriptional changes are key in AAA development (14). Among the numerous RNA modifications, m6A methylation is the most prevalent reversible and dynamic eukaryotic mRNA transcriptional modification, and it is also a key epigenetic mechanism in AAA (15).

2. m6A methylation

Methylation modification represents a considerable alteration to nucleic acids and proteins. It is associated with a number of pathological conditions, including cancer, the ageing process and Alzheimer's disease (16,17). DNA and histone methylation are among the most frequent methylation modifications. DNA methylation, which is the addition of methyl groups to DNA, is the primary mechanism by which gene transcription is repressed or silenced. By contrast, histone methylation refers to the process of methylation that occurs on the N-terminal arginine or lysine residues of H3 and H4 histones (18,19). This process is catalyzed by histone methyltransferases, which facilitate the transfer of a methyl group to the substrate, and mainly serves a role in forming heterochromatin, imprinting genes, inactivating the X-chromosome and regulating transcription (20). RNA methylation has been identified as a key factor in RNA metabolism and a multitude of cellular biological functions (21). The m6A modification is the most prevalent methylation modification observed in mRNAs with ~25% of mRNAs carrying ≥1 m6A site. These sites are enriched in proximity to the termination codon and 30 untranslated regions (UTRs) of human mRNAs and are present in a substantial number of mRNAs and long non-coding RNAs (lncRNAs) (22).

m6A RNA methylation is facilitated by a methyltransferase complex composed of methyltransferase 3-like (METTL3), METTL14 and Wilms' tumor 1-associated protein (WTAP) (23), and this complex has been observed to accelerate the processing time of mRNA precursors and their subsequent export from the nucleus. The methyltransferase complex is capable of regulating the eukaryotic transcriptome, influencing processes such as mRNA splicing, export, localization, translation and mRNA stability (24). The function of m6A is dependent on the presence of m6A readers, writers and erasers (25). In the nucleus, m6A may affect alternative splicing of pre-mRNAs, as well as the storage and export of mature mRNAs. The complexity of gene regulation mediated by RNA is influenced by the reversible and dynamic nature of distinct internal RNA modifications (26). m6A methylation modifications can affect the expression of target genes, thereby regulating a wide range of physiological processes, including self-renewal, invasion and proliferation (27). In addition to its involvement in neurodevelopmental regulation, several studies indicate that m6A carries out a pivotal role in tumor metabolism and growth (28,29). The expression and activity of writers and erasers mainly determine the abnormal m6A levels in cancer. The regulation of target mRNAs subsequent to modification is predominantly determined by readers (30). Additionally, m6A carries out a pivotal role in spermatogenesis, stem cell differentiation, immune response and other processes, e.g., regulating the stability of the internal environment (31,32). Previous research has identified m6A modifications as serving an important role in the development of cardiovascular diseases (33). Further studies are required to determine the role of m6A modifications in AAA pathophysiological processes, as this will provide new mechanistic and therapeutic insights (Fig. 1).

m6A writers. The m6A methyltransferase complex comprises METTL3, METTL14 and WTAP as its principal constituents.

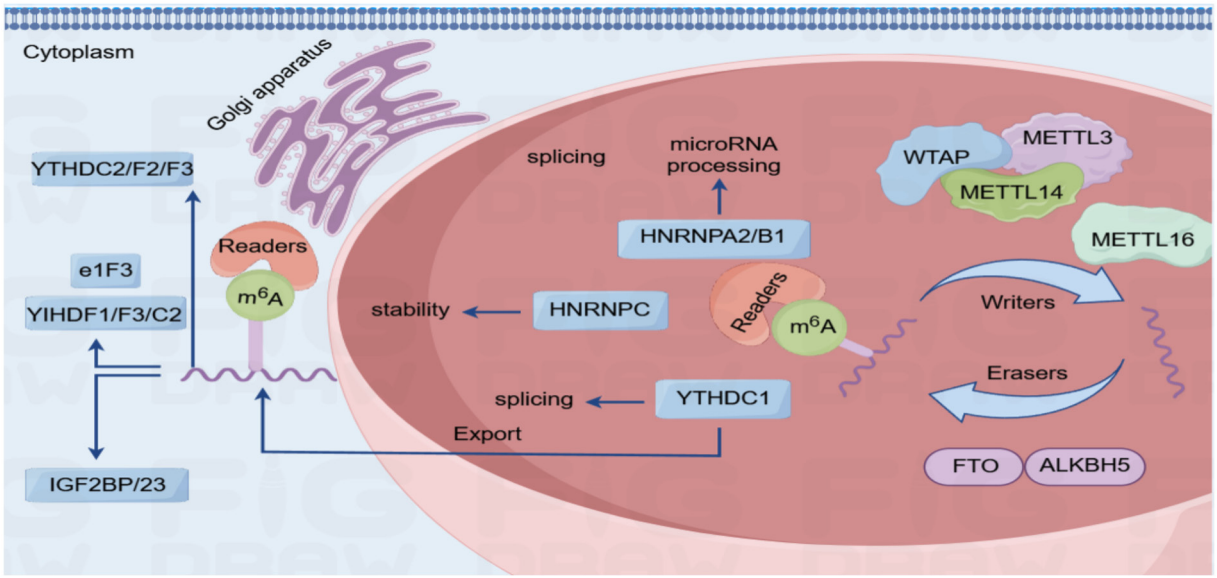

Figure 1. Process of m6A methylation. m6A methylation represents the most prevalent internal chemical modification in eukaryotic mRNA and is dynamically regulated by a tripartite enzymatic system (writers, erasers and readers) to fine-tune RNA metabolism and cellular responses. Mechanistic scheme: i) Methyltransferase complex (writers)-core components: METTL3 (catalytic subunit), METTL14 (structural scaffold) and WTAP (co-factor for localization). This complex catalyzes adenosine methylation at conserved RRACH motifs (R, purine; H, non-guanine base); ii) demethylases (erasers)-FTO and ALKBH5: Iron-dependent oxidases that remove m6A marks to ensure reversibility for adaptive gene regulation; and iii) m6A-binding proteins (readers), including the YTHDF family (YTHDF1/2/3): Direct mRNA fate. YTHDF1 enhances translation (ribosome recruitment), while YTHDF2 targets transcripts for decay (localization to processing bodies) and IGF2BP proteins stabilize mRNAs in an m6A-dependent manner. FTO, fat mass and obesity-associated protein; ALKBH5, ALKB homologue 5; METTL3, methyltransferase 3-like; IGF2BP, recombinant insulin like growth factor 2 mRNA binding protein 2k; YTHDF1, YTH domain family protein 1; YTHDC, YTH domain-containing protein 1; e1F3, eukaryotic translation initiation factor 3; HNRNPC, heterogeneous nuclear ribonucleoprotein C; m6A, N6-methyladenosine; WTAP, Wilms tumor 1 associated protein; HNRNPA2/B1, heterogeneous nuclear ribonucleoprotein A2/B1.

Catalytic activity resides in the METTL3-METTL14 dimeric unit, where METTL3 provides enzymatic function, while METTL14 stabilizes the structure and guides RNA binding. Together, they coordinate site-specific m6A deposition across RNA polymerase II transcripts. The METTL3-METTL14 heterodimer catalyzes the majority of m6A modifications in eukaryotic mRNAs (34). WTAP, a regulatory partner of this methyltransferase complex, recruits RNA substrates and directs methyl group deposition (26). In addition, KIAA1429 governs m6A installation at 3'UTRs through dual mechanisms (both dependent on and independent of m6A modification) to modulate RNA metabolism spanning splicing, maturation, translation and decay. These regulatory effects extend beyond mRNAs to include lncRNAs and circular RNAs (circRNAs) (35). In parallel, ZC3H13 promotes the nuclear translocation of the methyltransferase complex, functioning as an essential assembly cofactor (36). Vir-like m6A methyltransferase associated exhibits substrate specificity, preferentially marking mRNA regions near 3'UTRs and termination codons for methylation (37). Meanwhile, the METTL5-tRNA methyltransferase subunit 11-2 (TRMT112) complex generates unique m6A signatures in 18S rRNA, with METTL5 providing catalytic activity and TRMT112 serving as a structural scaffold (38). Beyond canonical methylation roles, METTL16 engages eukaryotic translation initiation factor 3 subunit a/b and ribosomal RNAs to coordinate translation initiation and mRNA-ribosome interactions (38).

m6A erasers. Fat mass and obesity-associated protein (FTO) and ALKB homologue 5 (ALKBH5) are the principal m6A demethylases. FTO was the first enzyme to be identified as an m6A demethylase. It is primarily located in nucleosomes (nuclear speckles), which are rich in RNA-binding proteins. It carries out an important role in the regulation of energy homeostasis, adipogenesis and cellular autophagy (39). The mechanism of FTO demethylation involves the catalysis of m6A oxidation, which produces intermediates that gradually demethylate and eventually form adenosine (40). The second m6A demethylase to be identified was ALKBH5, which has the capacity to interact directly with RNA in the nucleus, thereby demethylating m6A to adenosine without the production of intermediates (40,41). In addition to its role in mRNA stability, splicing and translation, ALKBH5 also carries out a key role in regulating the tumor immune microenvironment and mediating the effects of immunotherapy (42,43).

m6A readers. Methylated reading proteins are the executors of specific regulatory functions of m6A methylation modification. They are capable of recognizing and binding RNAs with the m6A modification, thereby mediating various processes related to RNA metabolic homeostasis (44). Different methylated reading proteins exercise different biological functions in m6A modification. Methylated reading proteins are primarily comprised of the YTH domain family (YTH) structural domain family [encompassing YTH N6-methyladenosine RNA binding protein F (YTHDF) 1, 2 and 3] and YTH domain containing 1-2 (including YTHDC1 and 2) (45). The YTH structural domains fulfill different functions through a family of YTH proteins that are expressed in different regions of the cell. YTHDC1 is widely expressed and mainly localized

in the nucleus, and YTHDF1-3 are mainly distributed in the cytoplasm and can facilitate translation of mRNAs containing m6A modifications (46). YTHDF1 has the capacity to regulate the translation initiation process through its interaction with initiation factors, thereby enhancing the translation efficiency of target RNAs. YTHDF2 is capable of selectively binding to RNAs bearing m6A modifications, thereby mediating a range of processes pertaining to RNA metabolic homeostasis. YTHDF2 selectively binds to RNAs with m6A modifications and transports them to the decay site to promote their degradation (40). YTHDC1 regulates the binding region of target RNAs by recruiting and regulating pre-mRNA splicing factors into the mRNA binding region of the target mRNAs. The mRNA binding regions regulate mRNA splicing (47). YTHDC2 regulates the stability of m6A-containing mRNAs by recruiting RNA degradation machinery (48). Furthermore, YTHDC2 enhances translational efficiency by directly recognizing mRNAs with m6A modifications (49). Additionally, it can accelerate mRNA decay by modifying the head region of the ribosomal 40S subunit, which promotes disassembly of the ribosomal mRNA complex (50) (Table I).

3. Mechanism of m6A methylation in AAA

Inflammation and the immune response. AAA pathogenesis involves a multifaceted interplay of inflammatory and immune mechanisms. Central to this process is ECM destabilization, driven by inflammatory cell-derived proteases that degrade vascular structural components. The compromised ECM integrity allows inflammatory cell migration through the vascular adventitia into the media, amplifying local inflammation (51). Platelet-mediated upregulation of osteopontin in macrophages and aortic tissues further exacerbates inflammation, vascular remodeling and leukocyte adhesion to the aneurysmal wall and intraluminal thrombus (ILT) (52). ILT perpetuates inflammation by generating a microenvironment enriched with neutrophils, proteases and reactive oxygen species (ROS), collectively weakening the aortic wall (53,54). Emerging insights highlight epigenetic regulation via m6A methylation in AAA progression. In atherosclerotic models, METTL14 silencing promotes anti-inflammatory M2 macrophage polarization, suppresses foam cell formation and attenuates migration by stabilizing Myd88 mRNA through m6A-dependent mechanisms (55). Meanwhile, activated macrophages are a major source of NF-κB, and the NF-κB signaling pathway is an important mechanism of action in AAA for the generation of inflammatory responses (56).

Notably, m6A modification is an upstream regulation of the NF-κB pathway, while it remains elusive whether m6A is able to influence the inflammatory response in AAA by regulating the NF-κB pathway (57). However, previous research on m6A methylation modification in AAA indicates that m6A methylation is capable of influencing the inflammatory response process. A notable correlation between the levels of macrophage infiltration and YTHDF3 expression was demonstrated by Zhong *et al* (58). Furthermore, METTL14 was also revealed to correlate with inflammatory infiltration and neovascularization in AAA (58). Cellular senescence and microRNA (miRNA or miR) dynamics further interconnect m6A with AAA pathology. Sirtuin 1 (SIRT1) mitigates aneurysm formation by inhibiting vascular senescence and pro-inflammatory factor secretion (59). Furthermore, miR34a has been demonstrated to increase aortic macrophage infiltration and the expression of age-associated pro-inflammatory secretory factors. Additionally, miR34a-mediated angiotensin (Ang) II-induced inflammation in the abdominal aorta has been observed following a direct reduction in SIRT1 expression (60). From a mechanistic perspective, elevated levels of AAA-related miR-34a are contingent upon increased expression of METTL3 in vascular smooth muscle cells (VSMCs). This is due to the capacity of METTL3 to enhance miR-34a maturation by recognizing DiGeorge syndrome critical region genes, thereby promoting m6A methylation (60). Receptor-interacting serine/threonine-protein kinase 3 (RIP3) is a kinase that carries out a role in the process of cellular necrosis and can initiate the cell necrosis process (61).

In the presence of the m6A reader YTHDF3, RIP3 has been shown to induce vascular endothelial cell necrosis. Furthermore, the debris produced by VSMC necrosis induces inflammatory factors in neighboring VSMCS and recruits monocytes or macrophages to the lesion site, which ultimately leads to the deterioration of AAA. In addition, mRNA expression of inflammatory factors [interleukin (IL)-6, TNF, C-C chemokine motif ligand 2 and IFN] was reported to be markedly elevated; however, it remains elusive whether m6A modifications regulate these cells (62). The three most prominent inflammatory cell types involved in the AAA aortic wall are immune-related lymphocytes, mast cells and macrophages (63). The pertinent lymphocyte populations implicated in the inflammatory process within the aortic wall are T and B lymphocytes. The most notable and prevalent cells within the aneurysmal wall are CD4+ T cells. These cells secrete a range of cytokines that control the dynamic metabolism of the ECM through macrophage incorporation, ECM regulation and protein hydrolase synthesis. Furthermore, T helper (Th) 1 is activated by IL-12 and secretes IFN-γ, TNF-α and TNF-β through the STAT4 and T-bet signaling pathways, thereby influencing macrophage activation and markedly contributing to AAA formation (64,65). Th2 represents the second important group of cells involved in the inflammatory process of AAA. These cells are regarded as anti-inflammatory cells (66). IL-4 stimulates Th2 cells, inducing the differentiation of CD4+ T cells into cells with a Th2 cell phenotype (67). m6A modification carries out an important role in the regulation of T-cell homeostasis and function. m6A not only has the potential to direct the differentiation of Th cells, but the abrogation of METTL3 in T cells also disrupts T-cell homeostasis (68). Mast cells can be activated by degranulation, which results in the release of proteases and inflammatory factors that promote AAA (69).

Furthermore, the key enzyme for m6A methylation, METTL3, has been demonstrated to regulate mast cell proliferation and effector functions by modulating the stability of IL-13 mRNA (70). In vascular Parkinson's disease, Qi *et al* (71) observed that Knockdown of the FTO gene mediated by m6A RNA methylation resulted in a reduction in the proportion of Th-cell subsets in lymphocytes. It should be noted that the different functional outcomes of m6A modifications depend largely on the cell type and cellular environment associated with different m6A 'readers' (72). Similarly, Fu *et al* (73)

Table I. Common types of m6A methylases and their functions.

Typology	Common genes/proteins	Functionality
m6A Writer	METTL3	An m6A methyltransferase that acts as an enzyme facilitator to form a METTL3-METTL14 heterodimer with METTL14 to catalyze m6A methylation modification of RNA *in vitro* and *in vivo*.
	METTL14	An m6A methyltransferase that acts as a heterologous activator to form a METTL3-METTL14 heterodimer with METTL3 to catalyze m6A methylation modification of RNA *in vitro* and *in vivo*.
	WTAP	Targets RNA and recruits the methyltransferase complex to RNA.
	KIAA1429	The ability to promote m6A modification of the 3'-UTR terminus not only affects the function of mRNAs, but also by affecting the function of lncRNAs and circRNAs.
	ZC3H13	Induction of methylase complex translocation into the nucleus as a novel cofactor for the m6A methyltransferase complex.
	VIRMA	A methyltransferase-associated protein that mediates preferential mRNA methylation near the 3'UTR and termination codon.
	METTL5	An m6A methyltransferase that acts as the catalytic subunit to form a METTL5-TRMT112 complex with TRMT112, which may be associated with ribosome generation and function.
	TRMT112	As a heterologous aptamer can form a METTL5-TRMT112 complex with METTL5, which may be related to ribosome production and function.
	METTL16	An m6A methyltransferase that promotes the assembly of translation initiation complexes and facilitates the translation of multiple mRNA transcripts.
m6A Eraser	FTO	An m6A demethylase, which catalyzes the oxidation of m6A to generate intermediates that are progressively demethylated and ultimately form adenosine, plays important functions in the regulation of energy homeostasis, adipogenesis and cellular autophagy.
	ALKBH5	An m6A demethylase that carries out a role in mRNA stability, splicing and translation; involved in nuclear export and processing of mRNAs and plays an important role in regulating the tumor immune microenvironment and mediating the effects of immunotherapy.
m6A Reader	YTHDF1	Contains the YTH structural domain, which regulates the translation initiation process by interacting with initiation factors, thereby improving the translation efficiency of the target RNA.
	YTHDF2	Contains a YTH structural domain that selectively binds RNA with m6A modifications and transports it to the decay site, promoting its degradation.
	YTHDF3	Contains the YTH structural domain, taking into account both YTHDF1 and YTHDF2 functions. It can collaborate with YTHDF1 and improve the translation efficiency of mRNA; it can also promote the degradation of m6A-containing mRNA by affecting YTHDF2-mediated RNA decay.
	YTHDC1	Contains a YTH structural domain that regulates mRNA splicing by over-recruiting and regulating pre-mRNA splicing factors into the binding region of the target mRNA.
	YTHDC2	Contains a YTH structural domain that recruits the RNA degradation machinery to regulate the stability of m6A-containing mRNAs; improves translational efficiency by directly recognizing mRNAs with m6A modifications; also promotes the disassembly of ribosomal mRNA complexes, thereby accelerating mRNA decay.

FTO, fat mass and obesity-associated protein; ALKBH5, ALKB homologue 5; METTL3, methyltransferase 3-like; YTHDF1, YTH domain family protein 1; YTHDC1, YTH domain-containing protein 1; m6A, N6-methyladenosine; WTAP, Wilms tumor 1 associated protein; KIAA1429, functional spliceosome-associated protein 121; ZC3H13, zinc finger CCCH-type containing 13 protein; VIRMA, Vir like M6A methyltransferase associated; METT3, methyltransferase 3.

identified notable differences in the expression of natural killer (NK) CD56-bright cells and immature dendritic cells between different m6A clusters in Gene Expression Omnibus (GEO) datasets. In a study conducted by Li *et al* (74) in GEO datasets, correlation analyses between the expression of AAA-associated m6A regulators and infiltrating immune cell scores in AAA tissues indicated that downregulation of METTL14 or heterogeneous nuclear ribonucleoproteins

C1/C2 and upregulation of RNA binding motif protein 15B may inhibit central memory T cell, macrophage and mast cell infiltration, and promote the aggregation of various immune cells such as Tγδ and NK CD56-bright cells. However, in the study by Wang *et al* (75), m6A methylation typing of patients with AAA based on m6A score was conducted and a positive correlation was identified between m6A scores and the majority of Th and effector T cells. Considerable differences were observed in various T cells across different m6A clusters, indicating a potential association between m6A methylation regulators and the effects of different T-cell profiles. This also indicates the potential for cellular heterogeneity and imbalanced m6A methylation expression levels in AAA, both at the pathological and molecular levels. It is evident that inflammation and immunity carry out a pivotal role in AAA development, and m6A may indirectly influence this process through its impact on inflammatory and immune cells.

Cell proliferation and apoptosis. From a physiological perspective, the abdominal aorta is an elastic artery comprising an intimal, a middle membrane and an outer membrane layers. The intima is a single layer of endothelial cells on connective tissue. The mesentery consists of ECM embedded with structural proteins (elastin and collagen). By contrast, the ectoderm consists of fibroblasts and collagen fibers (76). VSMCs are the major cellular component of the aortic mesentery. Their interactions with the mesenteric ECM help to maintain the structural and functional integrity of the aortic wall. The elastin of the mesentery is also synthesized primarily by VSMCs; thus, apoptosis of VSMCs and disruption of the ECM affect the structure of the entire aortic wall (77). Indeed, apoptosis of VSMCs in the inner layers of the aortic wall is an early marker of AAA pathogenesis. A reduction in VSMC density weakens the ability of the aortic wall to maintain its integrity and limits the ability of the stroma to be repaired, as VSMCs are essential for ECM regeneration. A reduction in VSMC density and ECM regenerative capacity make the aortic wall more susceptible to dilatation, which leads to the onset and progression of AAA (78).

Furthermore, following neovascularization, inflammatory cells such as macrophages migrate into the vessel wall, releasing pro-inflammatory cytokines and matrix metalloproteinases (MMPs), which stimulate smooth muscle cells to produce MMPs and other proteases. This results in the breakdown of collagen I and elastin, which in turn stimulates the migration of further inflammatory cells, thereby initiating a cascade of aortic wall breakdown (79). The degradation of the ECM and apoptosis of VSMCs are pivotal factors in the development of AAA from a histological perspective. m6A methylation affects the degradation of ECM and the apoptosis of VSMCs. In the context of intervertebral disc degeneration, Lei *et al* (80) demonstrated that m6A demethylation of Runx2 mRNA (a key regulator of skeletal development and homeostasis) promoted ECM degradation by upregulating MMPs. Zheng *et al* (81) also identified a role for the METTL14/METTL3 complex in mediating nucleosome assembly protein 1 like (NAP1L)2 apoptosis through m6A methylation of NAP1L2 mRNA in prostate cancer. m6A methylation of mRNA prompts NAP1L6 to interact with YinYang-1 (YY1), which promotes the transcription of MMP2 and MMP9, and ultimately activates the MMP signaling pathway. However, there is currently a lack of experimental evidence as to whether m6A methylation influences the degradation of ECM in cardiovascular diseases.

At least, the impact of m6A methylation on VSMCs has been established in the context of cardiovascular diseases. Zhao *et al* (82) demonstrated that METTL3 knockdown resulted in the attenuation of phosphatidylinositol 3-kinase (PI3K) mRNA, which inactivates PI3K/AKT signaling and inhibits VSMC phenotypic transition. Furthermore, Fang *et al* (83) reported that knockdown of METTL3 facilitated the proliferation of human aortic smooth muscle cells (HASMCs), whereas overexpression of METTL3 inhibited their proliferation. This phenomenon may be associated with the fact that METTL3 arrests HASMCs at the G2/M checkpoint and inactivates the phosphorylation of cell division cycle 2 (CDC2). Conversely, METTL3 knockdown was observed to enhance the migratory and synthetic phenotypes of HASMCs, whereas METTL3 gene overexpression inhibited the migratory and synthetic phenotypes of HASMCs. It is noteworthy that, in HASMCs overexpressing METTL3, the protein levels of MMP2, MMP7 and MMP9 were reduced, whereas the expression levels of tissue MMP inhibitor 3 were elevated.

Furthermore, Liao *et al* (84) observed that METTL3 promoted m6A methylation of lncRNA activated by DNA damage, an essential lncRNA for genomic stability, in a YTHDF2-dependent manner, thereby affecting VSMC proliferation in aortic coarctation. The current findings on m6A methylation modification in AAA similarly indicate that m6A methylation can influence vascular cell biological processes (85). RIP3 has been demonstrated to promote AAA progression by promoting smooth muscle cell necrosis. Furthermore, SMAD2/3-mediated increase in METTL3-METTL14 complex levels was revealed to enhance the m6A modification of RIP3 mRNA by promoting the binding between YTHDF3 and RIP3 mRNA, which in turn induced the necrosis of VSMCs and promoted AAA progression (62). This evidence suggests that m6A modification indirectly affects the ECM and thus has effects on AAA. In a previous study on colchicine-mediated retardation of AAA, colchicine increased global mRNA stability through the inhibition of METTL14/YTHDC1-mediated m6A modification. This ultimately prevented VSMC phenotypic transition and apoptosis, thereby slowing AAA progression (85). Furthermore, Xu *et al* (60) demonstrated that METTL3/YTHDC1-mediated m6A modification carried out a regulatory role in the biogenesis of circRBM33, which is derived from the exon of the RBM33 gene. Furthermore, knockdown of circRBM33 has been demonstrated to alleviate AAA by reducing ECM degradation. Consequently, the regulatory role of m6A modification on the proliferation and apoptosis of key VSMC cell types, as well as its effect on ECM degradation, may represent an important contributing factor in the development of AAA.

Regulation of miRNAs and circRNAs. miRNAs are evolutionarily conserved ncRNA molecules (~22 nucleotides) that post-transcriptionally modulate gene expression, targeting >1/3 of human genes (86,87). Biogenesis begins with RNA polymerase II transcribing primary miRNAs (pri-miRNAs), which are subsequently processed into precursor hairpins (pre-miRNAs) by the Drosha-DiGeorge critical region-8

(DGCR8) complex. Notably, a single pri-miRNA transcript may encode multiple distinct miRNAs (88). Notably, extracellular miRNAs exhibit remarkable stability in biofluids such as plasma, positioning them as promising biomarkers for detecting pathological states (89). In cardiovascular pathologies, including hypertension, heart failure and acute/chronic coronary syndromes, these small RNAs demonstrate diagnostic potential and therapeutic applicability through targeted gene regulation (90).

Therapeutic modulation of mRNA expression can be precision-engineered through synthetic miRNA mimics (upregulating targets) or anti-miR oligonucleotides (attenuating miRNA activity via sequence-specific binding) (91). In AAA, miRNAs emerge as master regulators coordinating ECM homeostasis, cellular reprogramming and tissue repair across vascular compartments (92). Genome-wide studies have revealed vascular-bed-specific miRNA signatures targeting endothelial cells, immune populations and, notably, VSMCs, whose dysregulation is directly associated with AAA pathomechanics (93). Mechanistically, miRNAs orchestrate aneurysm initiation/progression through three interlinked axes: i) VSMC plasticity control: Modulating proliferation/apoptosis balance and contractile-synthetic phenotype switching; ii) vasculo-inflammatory crosstalk: Regulating leukocyte infiltration and endothelial activation; and iii) MMP dysregulation: Driving collagen/elastin degradation thresholds (94). Emerging evidence indicates that miRNAs functionally crosstalk with pivotal disease-driving axes in AAA pathophysiology, particularly NF-κB (inflammatory activation), PI3K/AKT (cellular survival)/MAPK (proliferation-apoptosis balance), TGF-β/Wnt (matrix homeostasis) and p53/p21 (senescence regulation). This multi-axis regulatory network underpins aneurysm initiation and progression (95).

The regulatory landscape extends to circRNAs (covalently closed non-coding transcripts generated via exon-derived backsplicing of pre-mRNAs) (95). Distinguished by their notable stability (resistant to exonucleases) and evolutionary conservation, circRNAs exhibit tissue-enriched expression, yet remain detectable in the circulation. Functioning as miRNA sponges, they sequester miRNAs via complementary binding to derepress downstream targets, a competing endogenous RNA mechanism with therapeutic relevance (96). Notably, AAA-associated circRNAs (such as circCCDC66, circCBFB and hsa-circ000595) display altered expression profiles correlating with disease stages (97). m6A modification has been identified as a key factor contributing to miRNA biogenesis. A previous study by Alarcón *et al* (98) revealed that m6A was prevalent in pri-miRNA transcripts and that m6A levels were not markedly elevated by the presence of m6A.

Furthermore, the enrichment of m6A and the reduction of m6A levels resulted in the overall downregulation of the expression of most mature miRNAs (99). Downregulation of METTL3 also diminished the association between DGCR8 and target pri-miRNAs, which was accompanied by the nuclear accumulation of unprocessed pri-miRNAs. Furthermore, mutual regulation between m6A and circRNAs contributes to the biological properties and functions of circRNAs. It is notable that m6A modifications are not only widespread in circRNAs, but also that circRNAs exhibit different m6A patterns compared with mRNAs (100). During protein synthesis, circRNAs follow a non-canonical translation pathway that is positively regulated by m6A levels. Specifically, this m6A-driven translation is initiated through the binding of YTHDF3 to the translation initiation factors eIF4G2 and eIF3A (101). The impact of m6A modifications on miRNAs and circRNAs has been established in the context of cardiovascular disease. A study by Zhang *et al* (102) revealed that a reduction in the expression of METTL14 resulted in the inhibition of the binding of methylated RNAs to the RNA splicing-associated protein DGCR8. Furthermore, silencing of METTL14 was observed to markedly inhibit the expression of miR-19a, while promoting the expression of pre-miR-19a. Increased expression of METTL14 was observed to considerably increase the expression of DGCR8 and methylated m6A. Furthermore, silencing of miR-19a was observed to inhibit the proliferation and invasion of atherosclerotic vascular endothelial cells.

In a study on cardiac hypertrophy, Fang *et al* (103) identified circPan3 as a key inhibitor of cardiac hypertrophy through its targeting of the miR-320-3p/heat shock protein 20 axis. This regulatory mechanism was found to be mediated by the alkylated DNA repair protein ALKBH5 and to be associated with m6A methylation regulation. Previous findings on m6A methylation modification in AAA similarly revealed the effect of m6A on the regulatory role of miRNAs vs. circRNAs. Zhong *et al* (58) revealed that knockdown of METTL3 inhibited AAA formation by identifying that treatment of apolipoprotein E-deficient mice with Ang II, while METTL3 overexpression played the opposite role. This may be attributed to the METTL3-dependent methylation of m6A, which facilitates the maturation of pri-miR34a via DGCR8. In addition, overexpression of miR-34a was observed to notably reduce SIRT1 expression, thereby exacerbating the formation of AAA. Conversely, miR-34a deficiency was revealed to have the opposite effect. Furthermore, the protective effect of METTL3 deficiency on AAA formation was partially affected by knockdown of miR-34a or forced expression of SIRT1, respectively.

In a previous study, Xu *et al* (60) observed elevated m6A levels of circRBM33 in VSMCs with Ang II-induced AAA, which was indicative of its potential involvement in the disease process. METTL3 was observed to positively regulate circRBM33 expression, whereas YTHDC1 deficiency was revealed to decrease circRBM33 expression. Analysis revealed that METTL3/YTHDC1 regulated circRBM33 biogenesis in an m6A-dependent manner. This may be associated with the fact that METTL3/YTHDC1-mediated m6A modification regulates the biogenesis of circRBM33 from the exons of the RBM33 gene, thereby alleviating AAA development by reducing ECM degradation. Consequently, the effects of m6A methylation modifications on miRNA precursors and circRNAs are equally important for AAA development (Table II).

4. m6A methylation in AAA and potential clinical applications

The determination of medical management for AAA is based exclusively on the assessment of the aneurysm size, which is conducted through ultrasound or CT imaging. However, imaging techniques are retrospective and continuous AAA diameter changes require lengthy time intervals due to the

Table II. Identification and role of m6A methylation in abdominal aortic aneurysms.

First author/s, year	AAA-related m6A methylases	Main mechanisms	(Refs.)
He *et al*, 2019	YTHDF1, YTHDF3, FTO, METTL14	METTL14 is associated with inflammatory infiltration; FTO is associated with VSMC apoptosis; YTHDF3 is associated with macrophage infiltration	(59)
Zhong *et al*, 2020	METTL3	Promoting maturation of primary microRNAs	(58)
Li *et al*, 2021	METTL14, HNRNPC, RBM15B	Correlates with degree of immune infiltration	(74)
Fu *et al*, 2022	RBM15, WTAP, ALKBH5, IGFBP3	Immune infiltration; VSMC apoptosis	(73)
Wang *et al*, 2022	ALKBH5, HNRNPC, METTL14, YTHDF1, YTHDF2	Immune infiltration; inflammatory response	(75)
Li *et al*, 2023	METTL3-METTL14 complexes, YTHDF3	VSMC apoptosis; inflammatory response	(62)
Chen *et al*, 2024	METTL14/YTHDC1	VSMC phenotype switching and apoptosis; vascular inflammation	(85)
Xu *et al*, 2024	METTL3/YTHDC	Regulation of biogenesis from exon circRBM33 of the RBM33 gene	(88)

FTO, fat mass and obesity-associated protein; ALKBH5, ALKB homologue 5; METTL3, methyltransferase 3-like; IGFBP3, insulin-like growth factor binding protein 3; RBM15, RNA binding motif protein 15; YTHDF1, YTH domain family protein 1; YTHDC1, YTH domain-containing protein 1; HNRNPC, heterogeneous nuclear ribonucleoprotein C; m6A, N6-methyladenosine; WTAP, Wilms tumor 1 associated protein; VSMC, vascular smooth muscle cell.

slow progression of the disease. Consequently, biomarkers or combinations of biomarkers that predict the aneurysm growth rate offer numerous advantages in the clinical setting, both by facilitating clinical decision-making and evaluation of clinical trials of pharmacological interventions aimed at reducing aneurysm progression (104). Given the complexity and multifactorial nature of AAA, these biomarkers are involved in multiple pathways, including cardiovascular health, hemostasis, transport proteins, inflammation and immunity, renal function, cellular structure, and hormones and growth factors (105). MMP-9, IL-6, C-reactive protein (CRP), α1-antitrypsin, triglycerides, lipoprotein(a), apolipoprotein A and high-density lipoprotein have been identified as potential biomarkers associated with AAA progression (106). Furthermore, previous research has indicated that granzyme K, a proinflammatory factor within the granzyme family, may offer a promising avenue for diagnosing AAA and detecting rupture. Its combination with CRP or leukocytes represents a potential strategy for monitoring AAA (107). Consequently, a comprehensive understanding of the mechanisms underlying AAA onset and progression is key to facilitating the development of effective therapies.

Since it has become known that inflammatory cells and inflammatory mediators (including IL-1, IL-17, TGF-β and Ang II) are the predominant factors in the development of AAA (108), novel therapeutic approaches have emerged, including the immunosuppressive effect of cyclosporine-specific inhibitors on AAA progression, which has been previously demonstrated (109). In addition, the use of doxycycline, a broad-spectrum MMP inhibitor, has been revealed to slow the progression of AAAs by inhibiting the permanent dilation of the aorta caused by ECM degradation (110). Other approaches include the following: i) The reduction of inflammation in AAA tissues by Ang-converting enzyme inhibition (111); ii) the use of testosterone to inhibit AAA by modulating macrophages (112); iii) the use of statins to limit AAA progression through their anti-inflammatory and antioxidant properties; and iv) the use of metformin to mitigate AAA progression by attenuating vascular inflammation, ROS production and neovascularization (113). It is therefore important to investigate several pathways in order to improve the prognosis of this disease.

The structure and function of m6A methylation modifications affect not only chromatin regulation and transcriptional regulation, but also post-transcriptional regulation, which ultimately affects RNA metabolism and cellular function through different regulatory mechanisms (114). The current literature indicates that m6A methylation modifications are involved in the onset and progression of a variety of diseases, including the pathogenesis of cardiovascular diseases. It has been confirmed that m6A methylation influences the pathophysiology of cardiovascular disease by regulating cellular processes such as differentiation, proliferation, inflammation, autophagy and apoptosis (115), including the potential pathological mechanisms of METTL14-dependent m6A in vascular calcification (116), the existence of differential expression of genes in m6A-SNPs in coronary heart disease and the potential role of m6A in blood pressure regulation (117). Furthermore, m6A methylation plays a pivotal role in regulating the inflammatory response of macrophages, monocytes and endothelial cells. It also carries out a key part in the interplay between transcriptome modification regulation and inflammation in

cardiovascular disease, offering potential targets for disease diagnosis and treatment (116,117).

Aberrant expression of m6A methylation carries out a pivotal role in the interconnection between epigenetic modifications and immune infiltration in the pathogenesis of AAA. There are notable associations between AAA-related m6A regulators and key biological processes such as immunity, metabolism and autophagy. There is a close association between m6A methylation regulators and AAA immune cell infiltration, which may be a potential therapeutic target for the diagnosis and inhibition of AAA rupture (74,75). Emerging therapeutic strategies for AAA increasingly focus on m6A methylation regulators due to their dual roles in gene expression regulation and immune modulation. Pharmacological inhibition of m6A methyltransferases (such as METTL3) suppresses m6A deposition, thereby attenuating pro-inflammatory gene signatures and dampening immune-driven pathological cascades to impede AAA progression (62). Conversely, targeting m6A erasers (FTO and ALKBH5) stabilizes m6A-modified transcripts, which modifies immunomodulatory gene expression and alters immune signaling dynamics to exert therapeutic benefits (118). Additionally, intervening with m6A reader proteins (such as YTHDF2 and IGF2BP) provides a complementary approach, since modulating their binding activity reprograms m6A-mediated transcript fate, thus fine-tuning immune-related transcriptional programs and downstream effector responses (119).

Furthermore, miRNAs have emerged as a promising pharmacological tool for restoring cellular homeostasis and directing entire cellular pathways through interactions with a wide range of target genes. In light of the pivotal function of m6A-mediated miR-34a maturation in AAA development, miRNAs may offer a novel therapeutic target and diagnostic biomarker for AAA therapy (57). The inflammatory process in AAA is one of the key pathways, as this pathway possesses the most prognostic biomarkers (120,121). An understanding of the role of inflammation in AAA can facilitate the early detection and monitoring of the disease, which in turn can lead to an improvement in patient prognosis. However, the multiplicity of AAA mechanisms suggests that controlling pathways such as the genetic phenotype is equally important. By further elucidating the role of m6A methylation in AAA mechanisms, potential therapeutic targets can be identified through further investigation of the pathways involved in this disease, ultimately leading to the development of more effective treatments.

Although previous studies have found that m6A methylation has a considerable impact on the genetic risk of developing AAA, and a number of targets and regulators of m6A modification have been identified, the understanding of their functions and interaction mechanisms is still incomplete, and further functional studies are needed to clarify their exact roles in the relevant mechanisms. In addition, the current understanding of the dynamic regulatory mechanisms of m6A modification is still insufficient and further in-depth studies are needed to reveal the dynamic changes and regulation of m6A modification during AAA development. Finally, the application of the findings on m6A methylation regulators to clinical diagnosis and treatment is still challenging and further studies are needed to validate their feasibility and efficacy in patients with AAA.

5. Summary

AAA is a progressive dilatation of the abdominal aorta that is caused by a variety of lifestyle and genetic factors and has a high mortality rate. Despite considerable advances in imaging technology as well as open and endovascular repair techniques, pharmacological treatments that are capable of preventing the onset, dilatation and rupture of AAA and of treating AAA effectively in the perioperative period remain unavailable. This is due to the incomplete understanding of the biological mechanisms that underpin the disease. Genomic research has transformed the current understanding of the mechanisms that govern the development of multifactorial diseases such as AAA. This has been demonstrated through GWAS, which have identified AAA as a multifactorial, polygenic disease with epigenetic associations. Methylation represents the most extensively researched epigenetic mechanism. The methylation pattern constitutes a long-term genetic trait that induces alterations in gene transcription and is subject to influence from both genetic and environmental factors. The present review highlights the potential involvement of m6A methylation in the etiology of AAA from various perspectives.

m6A methylation, as a key form of RNA modification, carries out a pivotal role in the pathogenesis of AAA. The m6A modification affects the expression levels of AAA-related genes and participates in the regulation of various biological functions by regulating RNA transcription, splicing, degradation and translation processes. Previous studies have identified several key mediators and signaling pathways involved in m6A methylation during AAA pathogenesis, which may represent potential molecular targets for the control of AAA.

In light of the pivotal function of m6A modification in AAA, future research should investigate therapeutic strategies targeting m6A modification. This could entail regulating the expression and biological functions of AAA-related genes by inhibiting or promoting the activity of specific m6A modification-related proteins. The development of AAA is a multifactorial and complex process and it is important to develop standard protocols for early screening of AAA, treatment of lesion progression and prevention of AAA rupture, from the characterization and etiology of AAA to the in-depth molecular mechanisms of the AAA formation process. First, the regulatory mechanisms of m6A methyltransferases and m6A demethylases should be thoroughly investigated to understand their expression changes in AAA and their association with disease progression. Second, the functions of m6A-modified recognition proteins should be further explored to understand how they regulate m6A-modified target genes and immune signaling pathways. Finally, the interactions and synergistic regulation among m6A methylation regulators should be considered comprehensively to reveal the integrated effects of the whole regulatory network in AAA development. Furthermore, the association between the level of m6A modification and the clinical prognosis of AAA should be investigated to provide new insights and methodologies for the early diagnosis and treatment of AAA.

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Competing interests

The authors declare that they have no competing interests.

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